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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,384	04/27/2005	Monica Bequet Romero	976-19 PCT/US	3767

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,384	ROMERO ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70 and 80-100* is/are pending in the application.

4a) Of the above claim(s) *1-26, 28-34, 36-70 and 80-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,35 and 98-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-70 and 80-100 are pending.

2. Claims 1-26, 28-34, 36-70 and 80-97 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 27, 35, and newly added claims 98-100, drawn to an immunogenic composition comprising a VEGFR2 or fragments thereof and a mutant of VEGF-A, are being acted upon in this Office Action.

4. In view of the amendment filed 11/28/07, the following objections remain.

5. The computer readable form of the sequence listing filed 11/28/07 is acknowledged. However, said computer readable form of the sequence listing is not acceptable because the field <213> is invalid for all the sequences. It can be Artificial, Unknown or Genus species. See MPEP § 2424.02 and MPEP § 2431.

A substitute computer readable form (CFR) copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry, and a statement that the content of the paper and computer readable copies are the same and where applicable, include no new matter, as required by 37 C.F.R. 1.82(e) or 1.821(f) or 1.82(g) or 1.825(b) or 1.825(b).

6. The disclosure stands objected to under 37 CFR 1.821(d) because SEQ ID NO: is required for all amino sequences having four or more amino acids such as the ones listed in Tables 1 and 2 at pages 18-19. Amending the Tables to include SEQ ID NO: would obviate this objection.

7. The following new grounds of rejections are necessitated by the amendment filed 11/28/07.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 27 and 98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. **This is New Matter**.

The "VEGF2 polypeptide fragments corresponding to the *third* extracellular domain" in claim 27, part ii) and iii) has no support in the claims and the specification as originally filed. Applicants point to the specification at page 21, lines 9-15 and page 23, lines 17-24 for the amendment. However, the specification discloses only KDR1-3 which is from first through third extracellular domains of KDR (VEGFR2). The specification does not discloses VEGFR2 peptide fragments corresponding to just the *third* extracellular domain.

The "its aminoterminal fragments" in claim 27 part iii) has no support in the claims and the specification as originally filed.

The "p64K protein *aminoterminal fragments thereof*" in claim 27 part v) has no support in the claims and the specification as originally filed.

10. Claims 27 and 98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any p64K protein or its amino terminal fragments.

The specification discloses only p64K protein from the outer membrane of Neisseria meningitides that has adjuvant activity, see page 8, line 37.

The specification fails to disclose the structure associated with function of any "p64K protein" other than Neisseria meningitides, much less any N-terminal fragments thereof.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence. In this case, the specification discloses only one p64K protein from Neisseria meningitides outer membrane that has adjuvant activity.

Therefore, only adjuvant p64K protein from Neisseria meningitides outer membrane, but not the full breadth of the claim meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is indefinite because the metes and bounds of what would constitute the claimed composition cannot be determined. It is unclear whether the administering step is part of the claimed composition. Further, it is unclear what is incorporated into Neisseria meningitides outer membrane derived VSSP.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 27, 35 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/45018 (of record, published September 1999; PTO 892) in view of Stacker et al (J Biol Chemistry 274(49) 34884-92, December 1999; PTO 892) and Lu et al (J Biol Chemistry 275(19): 14321-14330, 2000; PTO 892).

For examination purpose, claim 35 is interpreted as an immunogenic composition comprising VEGFR2 polypeptide or fragments thereof and a mutant of VEGF polypeptide wherein the VEGF polypeptide is mutated to prevent binding to its receptor. A composition is a composition irrespectively of its intended use such as administered in the present of incorporated into Neisseria meningitidis outer membrane derived VSSP. Further, it is unclear whether VEGFR2 polypeptide or fragments thereof and a mutant of VEGF polypeptide are incorporated into VSSP, i.e., fused to VSSP or simply combined with VSSP.

The WO 99/45018 publication teaches an immunogenic composition for active immunization against angiogenesis associated antigens. The reference composition comprises immunogens such as vascular endothelial growth factor (VEGF) or antigenic fragment thereof (peptidomemetics which are mutant of VEGF) and KDR/flk-1 (VEGFR2) or antigenic fragments thereof combined with a pharmaceutically acceptable adjuvant (see page 8, second and third full paragraphs, page 11, last paragraph, page 16, last paragraph, in particular). The reference KDR/Flk-1 receptors are also known as VEGFR-2. The reference immunogens may be presented to the immune system by incorporated on the surface of recombinant bacterial cell such as Mycobacterium bovis (BCG), see paragraph bridging pages 17-18, or adsorbed onto a pharmaceutically acceptable adjuvant particles such as aluminum oxide or bacterial adjuvant BCG known in the art (see page 19, in particular).

The WO 99/45018 publication does not teach the VEGF polypeptide mutated to prevent binding to its receptor and the VEGFR2 polypeptide fragment corresponds to the third extracellular domain or corresponds to the first three extracellular domains.

However, Stacker et al teach VEGF (also known as VEGF-A) exists as a dimeric glycoprotein and binds to VEGFR-2 (also known as Flk-1 in mouse and KDR in human), see page 34884, in particular. Stacker et al teach various V3 domain mutants that lost binding to its VEGFR-2 such as Q36D, D40S, E43S, Y44H, K47S, E66H, E72T, K83A, H85G, Q86D, I90Y, and G91V using site directed mutagenesis as well as VEGF polypeptide Variable domain 3 that is responsible for binding to its receptor such as KPHQSQH has been changed to RSGDRPS (see page 34886, col. 1, Mutants of VEGF, Figure 1, page 34887, VEGF Mutants, Production and Quantification, in particular). Stacker et al teach mutant VEGF molecules in the bioassay demonstrated that the V3 domain between β strains 5 and 6 is critical for biding to and activation of VEGFR-2. In particular, the point mutations H85G and I90Y caused dramatic reductions in the level of activity seen the bioassay (see page 34890, col. 1, in particular).

Lu et al teach VEGFR2 polypeptide fragments such as monomeric KDR mutant containing only the first there N-terminal Ig domains (KDR1-3) (see page 14322, col. 1, Generation of KDR deletion mutants, in particular). Lu et al further teach KDR domain 3 is most critical for KDR/VEGF interaction and all neutralizing anti-KDR antibodies appear to bind to domain 3 or domains 1-3 for efficient inhibition of angiogenesis (see page 14328, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the VEGF antigenic fragment and the KDR/flk-1 (VEGFR2) fragment in the immunogenic composition of the WO 99/45018 publication for the VEGF-A V3 domain mutant that prevent binding to its receptor as taught by Stacker et al and the VEGFR2 polypeptide fragment corresponding to the first three extracellular domains of VEGFR-2 or just the third domain of VEGFR2 as taught by Lu et al to form a new immunogenic composition for passive immunization.

One having ordinary skill in the art would have been motivated to substitute the antigenic VEGF fragment of the WO 99/45018 publication for the V3 domain mutants that lost binding to its VEGFR-2 as taught by Stacker et al because Stacker et al teach the V3 domain between β strains 5 and 6 is critical for binding to and activation of VEGFR-2 since immunizing a subject with such peptide will elicit an immune response such as antibody response and/or cell-mediated response such as T-helper response inducing helper and cytotoxic T cell response in an animal against angiogenesis as taught by the WO 99/45018 publication (see page 1-6, in particular).

One having ordinary skill in the art would have been motivated to substitute the antigenic VEGF fragment of the WO 99/45018 publication for the KDR fragment corresponding to the first there N-terminal Ig domains (KDR1-3) or just the third domain of KDR because Lu et al teach KDR extracellular domain first through third domains or domain 3 is most critical for KDR/VEGF interaction and all neutralizing anti-KDR antibodies appear to bind to domains 1-3 for efficient inhibition of angiogenesis (see page 14323, paragraph bridging col. 1 and 2, in particular).

16. Claims 27, 98 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/45018 (of record, published September 1999; PTO 892) in view of Siemeister et al (J Biol Chemistry 273(18): 11115-11120, 1998; PTO 892) and Lu et al (J Biol Chemistry 275(19): 14321-14330, 2000; PTO 892).

The WO 99/45018 publication teaches an immunogenic composition for active immunization against angiogenesis associated antigens. The reference composition comprises immunogens such as vascular endothelial growth factor (VEGF) or antigenic fragment thereof (peptidomemetics which are mutant of VEGF) and KDR/flk-1 (VEGFR2) or antigenic fragments thereof combined with a pharmaceutically acceptable adjuvant (see page 8, second and third full paragraphs, page 11, last paragraph, page 16, last paragraph, in particular). The reference KDR/Flk-1 receptors are also known as VEGFR-2. The reference immunogens may be presented to the immune system by incorporated on the surface of recombinant bacterial cell such as Mycobacterium bovis (BCG), see paragraph bridging pages 17-18, or adsorbed onto a pharmaceutically acceptable adjuvant particles such as aluminum oxide or bacterial adjuvant BCG known in the art (see page 19, in particular).

The WO 99/45018 publication does not teach the VEGF-A polypeptide is a mutated $VEGF_{121}$ isoform that does not bind to its receptor and the VEGFR2 polypeptide fragment corresponds to the third extracellular domain or the VEGFR2 fragment corresponds to the first three extracellular domains.

However, Siemeister et al teach $VEGF_{121}$ isoform mutant such as $VEGF_{121}$ Δ1-17 that fails to bind to its KDR receptor (see page 1117, open diamonds in Figure 4B for KDR receptor and open diamonds in Figure 4A for Flt-1 receptor, page 11118, col. 2, first full paragraph, in particular). Siemeister et al teach the hydrophobic amino acids Val14, Val15, Phe17, and Met18 within the amphipathic α-helix near the amino terminus of $VEGF_{121}$ variant is essential for

formation of VEGF dimers and receptor binding (see abstract, paragraph bridging pages 11118 and 11119, in particular). Siemeister et al teach interference with the VEGF/VEGF receptor system is generally view as an attractive target for therapeutic intervention in a variety of human disease involving angiogenesis and agent interfering with the amino-terminal domain of VEGF121 may be a promising strategy for therapeutic intervention (see page 11119, last paragraph, in particular).

Lu et al teach VEGFR2 polypeptide fragments such as monomeric KDR mutant containing only the first there N-terminal Ig domains (KDR1-3) (see page 14322, col. 1, Generation of KDR deletion mutants, in particular). Lu et al further teach KDR domain 3 is most critical for KDR/VEGF interaction and all neutralizing anti-KDR antibodies appear to bind to domain 3 or domains 1-3 for efficient inhibition of angiogenesis (see page 14328, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute VEGF antigenic fragment and KDR/flk-1 (VEGFR2) fragment in the immunogenic composition of the WO 99/45018 publication for the $VEGF_{121}$ Δ1-17 mutant that fails to bind to its receptor as taught by Siemeister et al and the VEGFR2 polypeptide fragment corresponding to the first three extracellular domains of VEGFR-2 or just the third domain of VEGFR2 as taught by Lu et al to form a new immunogenic for active immunization against angiogenesis associated antigens.

One having ordinary skill in the art would have been motivated with the expectation of success to substitute the antigenic VEGF fragment of the WO 99/45018 publication for the $VEGF_{121}$ Δ1-17 mutant that lost binding to its VEGFR-2 as taught by Siemeister et al because this $VEGF_{121}$ Δ1-17 mutant would interfere with the VEGF/VEGF receptor system is generally view as an attractive target for therapeutic intervention in a variety of human disease involving angiogenesis and agent interfering with the amino-terminal domain of VEGF121 may be a promising strategy for therapeutic intervention as taught by Siemeister et al (see page 11119, last paragraph, in particular). By analogy, immunogenic composition comprising $VEGF_{121}$ Δ1-17 mutant that generates antibody that binds to this $VEGF_{121}$ Δ1-17 mutant would also interfere with the VEGF121 binding to its VEGF receptor.

One having ordinary skill in the art would have been motivated to substitute the antigenic VEGF fragment of the WO 99/45018 publication for the KDR fragment corresponding to the first there N-terminal Ig domains (KDR_{1-3}) or just the third domain because Lu et al teach KDR

domain 3 is most critical for KDR/VEGF interaction and all neutralizing anti-KDR antibodies appear to bind to this third domain or the KDR domains 1-3 for efficient inhibition of angiogenesis (see page 14323, paragraph bridging col. 1 and 2, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to make an immunogenic composition comprising mutant $VEGF_{121}$ isoform that does not bind to its receptor and the VEGFR2 polypeptide fragment corresponds to the third extracellular domain or the VEGFR2 fragment corresponds to the first three extracellular domain because the WO 99/45018 publication teaches immunizing a subject with such composition will elicit an immune response such as antibody response and/or cell-mediated response such as T-helper response inducing helper and cytotoxic T cell response in an animal against angiogenesis (see page 1-6, in particular).

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
February 29, 2009